

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654****REMARKS**

Claims 16, 20-22, 24-31, 33-35, and 37-40 are currently pending. Claims 16, 34 and 37 have been amended to more precisely claim the derivatives of the peptide stabilizers. Support for this amendment can be found, e.g., in paragraphs 27 and 28 of the published patent application. No new matter has been added. In the Final Office action, the Office indicated that claims 38-40 were withdrawn from further consideration as being drawn to a nonelected species.

1. Rejection of the Claims under 35 U.S.C. §103(a) (¶3)

Reconsideration is respectfully requested of the rejection of claims 16, 21, 22, 24-26, 30, 31, 33, 34 and 37 under 35 U.S.C. § 103(a) as being obvious over Sato, et al. (U.S. Patent Application Publication No. 2003/0092622).

Claim 16 is directed to a stable pharmaceutical composition comprising erythropoietin and a peptide stabilizer, which is free of serum albumin. The peptide stabilizer is selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof. As currently amended, the derivatives are selected from the group consisting of acylated, alpha-keto and salt forms of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala.

Sato et al. describe a protein formulation containing a stabilizer selected from tryptophan, a tryptophan derivative or a salt thereof. The addition of the stabilizer is said to promote long-term storage stability of the protein formulation. One of the proteins that may be stabilized using the method described by Sato et al. is erythropoietin.

As discussed above, the only stabilizers that Sato et al. describe are tryptophan, tryptophan derivatives, and salts thereof. Paragraph [0047] of Sato, et al. lists a large number of salts and derivatives that can be used, but, as can be seen from that list, the stabilizer described by Sato et al. always comprises the amino acid tryptophan or a derivative or salt thereof. Sato et al. do not suggest the use of any of the peptides listed in

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

claim 16. In addition, there is no suggestion or motivation in Sato, et al. to use any of the peptides listed in claim 16 as stabilizers.

The Office indicated that the obviousness rejection over Sato et al. was maintained in view of the fact that the Trp-based stabilizers of US 2003/0092622 and WO 01/64241 can be considered to be derivatives of the peptide stabilizers described in the present invention. Specifically, the Office has stated that the tryptophan-based stabilizers of Sato et al. constitute "derivatives" of the peptide stabilizers claimed in the present application because of similarity in structure (i.e., dipeptides or tripeptides having at least one amino acid in common) and ability to stabilize protein compositions. In support of its argument, the Office cited three patents and patent publications: U.S. Patent No. 6,624,289 (Bajaj), U.S. Patent No. 6,538,028 (Pierson et al.) and U.S. Patent Application No. 2005/0288222 (Heyward et al.). According to the Office, these documents were used to show that the term "derivative" is interpreted broadly in the art and that a peptide derivative does not have to have the same number of amino acids as the peptide or even be a peptide, i.e., it could be a non-peptidic derivative.

Applicants have amended independent claims 16, 34 and 37 to further define derivatives as those which are acylated, alpha-keto or salt forms of the claimed peptide stabilizers. The derivatives now claimed do not include, for example, the Trp-Gly tryptophan derivative of Sato et al.

The specification of the present application states the following about the derivatives that can be used:

Non-naturally occurring amino acids include, but are not limited to, amino acid derivatives and analogs. Non-limiting examples of amino acid derivatives include selenomethionine, telluro-methionine, and p-aminophenylalanine, fluorinated amino acids (e.g., fluorinated tryptophan, tyrosine and phenylalanine), nitrophenylalanine, nitrobenzoxadiazolyl-L-lysine, deoxymethylarginine, and cyclohexylalanine. Amino acid analogs include chemically synthesized compounds having properties known in the art to be characteristic of amino acids, examples of which include, e.g., the tryptophan "analog" b-selenolo[3,2-b]pyrrolylalanine and the proline "analog" thiaproline (1,3-thiazolidine-4-carboxylic acid). Additional amino acid derivatives include amino acid salts, acylated amino acids, and alpha-keto amino acids.

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

By way of example and not of limitation, a dipeptide can contain an L-amino acid and a D-amino acid, an L-amino acid and an amino acid salt, a D-amino acid and an amino acid analog, an L-amino acid and an acylated amino acid, an L-amino acid and an alpha-keto amino acid, an acylated amino acid and an alpha-keto amino acid, two acylated amino acids, two L-amino acids, two amino acid salts, etc. (Paragraphs 27 & 28 of the patent application publication; emphasis added)

Therefore, one skilled in the art would recognize that the derivatives of the pending non-withdrawn claims are dipeptides or tripeptides which contain one or more amino acids salts, acylated amino acids, and alpha-keto amino acids. By way of example and as indicated above, derivatives of dipeptides such as, e.g., Gly-Gly, Gly-Tyr, Gly-Phe can include, e.g., glycine and glycine salt, glycine and fluorinated tyrosine, and glycine and p-aminophenylalanine, respectively. As another example, the derivatives of these peptides can include glycine salt and acylated glycine, alpha-keto glycine and tyrosine, and glycine and phenylalanine salt, respectively.

Based on the foregoing, applicants submit that the derivatives of the peptide stabilizers of the present invention are different than the peptide stabilizers of Sato et al. Furthermore, applicants submit that based on the teachings of Sato et al., a skilled artisan would not have been motivated to use the peptides or peptide derivatives of claim 16 to stabilize erythropoietin. In addition, there would have been no reasonable expectation that the peptides or peptide derivatives of claim 16 could be used successfully as erythropoietin stabilizers based on Sato et al. teachings.

With respect to serum albumin, Sato et al. state that the formulations may be substantially free of serum albumin, whereas the formulation of claim 16 is free of serum albumin. The Office noted that it would have been *prima facie* obvious to omit serum albumin from Sato et al. formulations because it is preferable in pharmaceutical arts to minimize the number of ingredients in order to reduce chances for any side effects. However, serum albumin has been used in protein formulations, including erythropoietin, because it stabilized the protein against physical and chemical changes that the protein can undergo in solution. Thus, even if one skilled in the art were motivated to remove serum albumin to minimize the number of components in a pharmaceutical formulation,

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

that skilled person would not have a reasonable expectation of success in maintaining the stability of the formulation if the stabilizer is entirely removed. Accordingly, for all of the above reasons, applicants submit that claim 16 is non-obvious and patentable over Sato et al.

Claims 21, 22, 24-26, 30, 31 and 33 depend either directly or indirectly from claim 16 and are thus patentable for the same reasons as claim 16, as well as for the additional elements they require.

Claim 34 is similar to amended claim 16, and further comprises a polyoxyalkylene sorbitan fatty acid ester. Claim 34 is patentable for the same reasons as set forth above for claim 16, as well as for the additional elements it requires.

As amended, claim 37 is similar to claim 16, and further requires that the composition be for administration by parenteral injection. Claim 37 is thus patentable for the same reasons as set forth above for claim 16, as well as for the additional elements it requires.

2. Rejection of the Claims Under 35 U.S.C. §103(a) (¶4)

Reconsideration is respectfully requested of the rejection of claims 24-29 and 35 under 35 U.S.C. § 103(a) as being obvious over Sato, et al. (U.S. Patent Application Publication No. 2003/0092622) in view of WO 02/14356.

Claims 24-29 and 35 depend either directly or indirectly from claims 16 and 34, respectively, as discussed above.

Sato et al. is discussed above. WO 02/14356 discloses the preparation of erythropoietin omega and methods of treatment using the same.

The Office alleged that it would have been obvious to stabilize the erythropoietin omega of WO 02/14356 with a peptide stabilizer described by Sato, et al. to preserve its therapeutic activities.

WO 02/14356 does not teach or even mention that erythropoietin omega can be formulated using peptide stabilizers. There is therefore no motivation in the cited references to combine the teachings of Sato, et al. and WO 02/14356, absent the

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

hindsight analysis of the applicants' disclosure. The Office alleged that the motivation to combine references can be found in the prior art as a whole because WO 02/14356 teaches a specific form of erythropoietin and Sato et al. list that erythropoietin can be stabilized with tryptophan, derivative thereof or salt thereof. Applicants note that even if the teachings of Sato et al. were combined with the teachings of WO 02/14356, one skilled in the art would still not have arrived at the present invention, i.e., a stable pharmaceutical composition of erythropoietin comprising a peptide stabilizer selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof, which is free of serum albumin and wherein the derivatives are selected from the group consisting of acylated, alpha-keto and salt forms of said peptide stabilizers. Sato et al. and WO 02/14356 thus either alone or in combination fail to teach or suggest all the limitations of the claims. Claims 24-29 and 35 are thus patentable over the combination of Sato et al. and WO 02/14356.

3. Rejection of the Claims Under 35 U.S.C. §103(a) (¶5)

Reconsideration is respectfully requested of the rejection of claims 16, 21, 22, 24-26, 30, 31, 33, 34, and 37 under 35 U.S.C. §103(a) as being obvious over WO 01/64241. As stated in the Office action, WO 01/64241 is the equivalent to the Sato et al. reference discussed above, only published in Japanese. Applicants therefore submit that claims 16, 21-22, 24-26, 30-34, and 37-40 are patentable over WO 01/64241, for the same reasons as set forth above in §1 of this response, with respect to Sato et al.

4. Rejection of the Claims Under 35 U.S.C. §103(a) (¶6)

Reconsideration is respectfully requested of the rejection of claims 24-29 and 35 under 35 U.S.C. §103(a) as being obvious over WO 01/64241 in view of WO 02/14356. As mentioned above, WO 01/64241 is equivalent to the Sato et al. reference discussed above, only published in Japanese. Applicants therefore submit that claims 24-29, 35 and new claims 38-40 are patentable over WO 01/64241 in view of WO 02/14356, for the

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

same reasons as set forth above in §2 of this response, with respect to Sato et al. and WO 02/14356.

5. Rejection of the Claims Under 35 U.S.C. §103(a) (17)

Reconsideration is respectfully requested of the rejection of claims 16, 20-22, 24, and 37 under 35 U.S.C. § 103(a) as being obvious over Cormier, et al. (U.S. Patent Application Publication No. 2002/0058608).

Cormier et al. teach a buffered aqueous formulation for transdermal electrotransport delivery, which comprises a therapeutic agent buffered with a dipeptide buffer. The list of proteins and peptides that are said to be applicable embraces over 90 agents, including erythropoietin (see paragraph [0034]). However, Cormier et al. only exemplified formulations of human growth hormone, synthetic radiolabeled decapeptide (DECAD), and small molecular weight drug-like compounds such as trimethylammonium bromide (TMAB) and sodium methanesulfate (SMS) in the working examples of the patent. Furthermore, according to Cormier, et al., the dipeptide buffer is preferably selected from a list of over 55 dipeptides, including Gly-Asp and Gly-His (see paragraph [0014]). No tetrapeptides or pentapeptides are exemplified.

The Office has stated that it would have been obvious to administer EPO using the Gly-His buffer of Cormier et al. because the reference discloses that EPO is a protein which can be usefully administered in their formulations. Cormier et al. fail to teach or suggest the use of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-Ala, Ala-Gly, Ala-Ala, mixtures thereof or derivatives thereof as buffers, wherein the derivatives consist of acylated, alpha-keto and salt forms of said peptide stabilizers. The only dipeptides listed in claim 16 that are specifically disclosed by Cormier et al. are Gly-His and Gly-Asp. Applicants further note that in order to arrive at a composition comprising erythropoietin and Gly-His, one skilled in the art must pick and choose from several options in Cormier et al. Specifically, one skilled in the art would have to choose erythropoietin from a laundry list of over 90 possible drugs listed by Cormier, et al. After deciding to include erythropoietin, one skilled in the art would then have to choose Gly-His from over 55

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

possible dipeptides listed by Cormier et al. Furthermore, these choices must be made absent any teaching or suggestion in Cormier et al. as to the specific combination of erythropoietin and Gly-His (or Gly-Asp). As such, applicants submit that there is no suggestion or motivation in Cormier et al. to formulate a composition comprising the specific combination of erythropoietin and Gly-His (or Gly-Asp) from about 5,000 combinations that could have been made.

Furthermore, even if one skilled in the art attempted to formulate a composition comprising erythropoietin and Gly-His (or Gly-Asp), that skilled person would not have arrived at a stable pharmaceutical composition as defined in claim 16 which is free of serum albumin. There is no teaching or suggestion in Cormier et al. that their compositions are formulated so as to be free of serum albumin. The Office has stated that since Cormier et al. do not mention serum albumin, it can be assumed that their compositions do not comprise serum albumin. In addition, the Office noted that assuming anything else would be against established patent laws since it would allow for a prior art formulation to be re-patented an indefinite number of times.

In response, applicants note that a pharmaceutical composition which is free of serum albumin is an essential component of the present invention. Furthermore, the use of peptide stabilizers of claim 16 not only allows for efficient protein stabilization but also avoids a complicated process used to remove viral contamination, which is performed when a pharmaceutical formulation contains serum albumin. Applicants also note that all of the claim limitations need to be considered when evaluating patentability of a claim. The fact that Cormier et al. are silent about the presence of serum albumin does not mean that the compositions of Cormier et al. are necessarily free of serum albumin, especially in view of the fact that serum albumin was commonly used as a protein stabilizer. As such, applicants submit that Cormier et al. fail to teach or suggest all the limitations of claim 16.

Claims 20-22, and 24 depend either directly or indirectly from claim 16 and are therefore patentable over Cormier, et al. for the same reasons as set forth above for claim 16, as well as for the additional elements they require.

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

As discussed above, amended claim 37 is similar to claim 16, except that it further requires the composition to be for administration by parenteral injection. Claim 37 is thus patentable for the same reasons as set forth above for claim 16. In addition, the composition of amended claim 37 is for administration by parenteral injection in contrast to the formulations of Cormier et al., which are for transdermal delivery. There is no teaching or suggestion in Cormier et al. of using their formulations for administration by parenteral injection, nor is there any teaching or suggestion of how a formulation for parenteral injection would be prepared or stabilized. In fact, if anything, Cormier et al. teach away from administration by parenteral injection. For example, Cormier et al. specifically point out drawbacks of parenteral injection, stating:

Polypeptide and protein molecules are highly susceptible to degradation by proteolytic enzymes in the gastrointestinal tract and are subjected to an extensive hepatic metabolism when taken orally. Thus, these substances usually require parenteral administration to achieve therapeutic levels in the patient's blood. The most conventional parenteral administration techniques are hypodermic injections and intravenous administration. Polypeptides and proteins are, however, inherently short acting in their biological activity, requiring frequent injections, often several times a day, to maintain the therapeutically effective levels needed. Patients frequently find this treatment regimen to be inconvenient and painful. Such therapy also includes risk of, e.g., infection. (p. 1, ¶0007)

One skilled in the art would not have been motivated by Cormier et al. to modify the formulations of Cormier et al. for administration by parenteral injection. Nor would Cormier et al. have provided any guidance to one of ordinary skill as to how to stabilize a parenteral pharmaceutical composition containing erythropoietin since Cormier et al. would only guide one in selecting an appropriate pH stable buffer for transdermal electrotransport of a drug. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Claim 37 is thus also patentable over the cited reference as it fails to teach or suggest such a composition for parenteral injection.

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654****6. Rejection of the Claims Under 35 U.S.C. § 103(a) (¶8)**

Reconsideration is respectfully requested of the rejection of claims 24-29 under 35 U.S.C. § 103(a) as being obvious over Cormier et al. (U.S. Patent Application Publication No. 2002/0058608) and further in view of WO 02/14356.

Claims 24-29 depend either directly or indirectly from claim 16, which is discussed above. Cormier et al. and WO 02/14356 are discussed above.

The Office has alleged that it would have been obvious to formulate the erythropoietin omega of WO 02/14356 in the compositions of Cormier et al. because it would be desirable to administer erythropoietin omega iontophoretically, and Cormier et al. teach administration of a wide range of proteins. Claim 16 is patentable over Cormier et al. for the reasons set forth above. The deficiencies of Cormier et al. are not overcome by WO 02/14356 since, as discussed above, WO 02/14356 does not even disclose or suggest that erythropoietin omega can be formulated using peptide stabilizers. Therefore, even if one were to combine Cormier et al. and WO 02/14356, one still would not arrive at a composition as defined by claim 16. Applicants thus submit that claim 16 is patentable over Cormier et al. and WO 02/14356 either alone or in combination. Since claims 24-29 depend either directly or indirectly from claim 16, they are patentable for the same reasons as set forth above for claim 16.

7. Rejection of the Claims Under 35 U.S.C. § 103(a) (¶9)

Reconsideration is respectfully requested of the rejection of claims 30-31 and 33-34 under 35 U.S.C. § 103(a) as being obvious over Cormier et al. (U.S. Patent Application Publication No. 2002/0058608) and further in view of Holladay et al. (U.S. Patent No. 6,328,728).

Claims 30-31 and 33 depend either directly or indirectly from claim 16, which is discussed above, and further call for the composition to comprise a surfactant.

Cormier, et al. is discussed above.

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

Holladay et al. teach a method of enhancing electrotransport delivery of an active agent, such as a protein in the presence of at least one electrotransport enhancer selected from nonionic surfactants, zwitterionic surfactants lacking a net charge, and mixtures thereof, such as polyoxyethylene (20) sorbitan monolaurate or polyoxyethylene (20) sorbitan monopalmitate.

The Office has stated that it would have been obvious to one of ordinary skill in the art to include a surfactant of Holladay et al. in the compositions of Cormier et al. to increase the flux or decrease biodegradation of proteins during electrotransport delivery.

Claim 16 is patentable over Cormier et al. for the reasons set forth above. The deficiencies of Cormier et al. are not cured by the teachings of Holladay et al., since Holladay et al. do not teach or suggest the use of peptides in their compositions. Rather, Holladay et al. merely teach enhancing electrotransport delivery of an active agent, such as a protein, in the presence of at least one electrotransport enhancer, such as certain surfactants. Motivation for formulating a composition comprising the specific combination of erythropoietin and one of the peptides listed in claim 16 can thus not be found in Holladay et al.

Claims 30-31 and 33 depend either directly or indirectly from claim 16 and are thus patentable for the same reasons as set forth above for claim 16, as well as for the additional elements they require.

As discussed above, claim 34 is directed to a stable pharmaceutical composition comprising erythropoietin, a polyoxyalkylene sorbitan fatty acid ester, and a peptide stabilizer. The peptide stabilizer is selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof, wherein the composition is free of serum albumin and wherein the derivatives are selected from the group consisting of acylated, alpha-keto and salt forms of said peptide stabilizers.

For the reasons set forth in §5 above with respect to Cormier et al., there is no suggestion or motivation in Cormier, et al. to formulate a composition comprising the specific combination of erythropoietin and Gly-His or Gly-Asp (or Gly-Gly, Gly-Gly-

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

Gly, Gly-Tyr, Gly-Phe, Gly-Ala, Ala-Gly, or Ala-Ala derivatives thereof or mixtures thereof, which are not even mentioned in Cormier et al. (as buffers). The deficiencies of Cormier et al. are not cured by the teachings of Holladay et al., since, as discussed above, Holladay, et al. do not teach or suggest the use of peptides in their compositions.

Furthermore, Cormier et al. do not disclose that their composition may comprise a polyoxyalkylene sorbitan fatty acid ester, as required by claim 34. At most, Cormier et al. state that surfactants may be used as a penetration enhancer to facilitate absorption through the skin (p. 4, ¶0035). Holladay, et al. disclose a list of over 35 non-ionic and zwitterionic surfactants that may be used as penetration enhancers, including polyoxyethylene (20) sorbitan monolaurate and polyoxyethylene (20) sorbitan monopalmitate. In order to formulate a composition comprising erythropoietin and Gly-His (or Gly-Asp) and a polyoxyalkylene sorbitan fatty acid ester, one skilled in the art would therefore have to choose erythropoietin from a laundry list of over 90 possible drugs listed by Cormier et al. and Holladay et al., and after deciding to include erythropoietin, one skilled in the art would then have to choose Gly-His or Gly-Asp from over 55 possible dipeptides listed by Cormier et al., and would then have to further choose a polyoxyalkylene sorbitan fatty acid ester from over 35 possible surfactants listed by Holladay et al. Furthermore, these choices must be made absent any teaching or suggestion in Cormier et al. or Holladay et al. as to the specific combination of erythropoietin, Gly-His or Gly-Asp, and a polyoxyalkylene sorbitan fatty acid ester. As such, applicants submit that there is no suggestion or motivation in Cormier et al. or Holladay et al. to formulate a composition comprising the specific combination of erythropoietin, Gly-His or Gly-Asp, and a polyoxyalkylene sorbitan fatty acid ester since these combinations are only two of over 100,000 combinations that could have been made.

Furthermore, even if one skilled in the art attempted to formulate a composition comprising erythropoietin and Gly-His or Gly-Asp and a polyoxyalkylene sorbitan fatty acid ester based on the teachings of Cormier et al. and Holladay et al., one may still not have arrived at a stable pharmaceutical composition as defined in claim 34, since there is

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

no teaching or suggestion in Cormier et al. or in Holladay et al. that their compositions are formulated so as to be free of serum albumin, as required by claim 34. Neither Cormier et al. nor Holladay et al. mentions serum albumin. As discussed above, just because serum albumin is not mentioned by Cormier et al. or Holladay et al. does not mean that the compositions of Cormier et al. or Holladay et al. are necessarily free of serum albumin. As such, applicants submit that Cormier et al. and Holladay et al., either alone or in combination, fail to teach or suggest all the limitations of claim 34.

8. Rejection of the Claims Under 35 U.S.C. § 103(a) (¶10)

Reconsideration is respectfully requested of the rejection of claim 35 under 35 U.S.C. §103(a) as being obvious over Cormier et al. (U.S. Patent Application Publication No. 2002/0058608) in view of WO 02/14356 and further in view of Holladay et al. (U.S. Patent No. 6,328,728).

Claim 35 depends from claim 34, discussed above, and further states that the erythropoietin is erythropoietin omega. For the reasons previously noted, claim 34 is patentable over Cormier et al. and Holladay et al. either alone or in combination.

The Office has stated that it would have been obvious to one of ordinary skill to include the surfactant of Holladay et al. in the composition of Cormier et al. as modified to include the EPO omega of WO 02/14356 to increase the flux or decrease biodegradation of proteins during electrotransport delivery. With respect to Cormier et al. and Holladay et al. applicants again note that there is no suggestion or motivation in Cormier et al. or Holladay et al. to formulate a composition comprising the specific combination of erythropoietin, Gly-His or Gly-Asp (or Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-Ala, Ala-Gly, or Ala-Ala, derivatives thereof or mixtures thereof, wherein the derivatives are selected from the group consisting of acylated, alpha-keto and salt forms of said peptide stabilizers), and a polyoxyalkylene sorbitan fatty acid ester. Nor do Cormier et al. and Holladay et al., either alone or in combination, teach or suggest all the limitations of claim 34. The deficiencies of Cormier et al. and Holladay et al. are not overcome by WO 02/14356 since, as discussed above, WO 02/14356 does not even

DI-5954 (BXTR 9004.6)
PATENT**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

disclose or suggest that erythropoietin omega can be formulated using peptide stabilizers. Furthermore, even if one were to combine Cormier et al., Holladay et al., and WO 02/14356, one still would not arrive at a composition as defined by claim 35. Applicants thus submit that claim 35 is patentable over Cormier et al., Holladay et al., and WO 02/14356 either alone or in combination.

DI-5954 (BXTR 9004.6)
PATENT

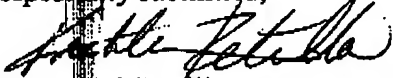
**REPLY UNDER 37 CFR 1.116-EXPEDITED PROCEDURE-
TECHNOLOGY CENTER 1654**

CONCLUSION

In view of the foregoing comments, Applicants respectfully request entry of the amendments and solicit allowance of the claims.

Please charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,


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